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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,612	11/13/2001	Alesandro Massimo Gianni	GIANNI=1	5788

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EXAMINER

HAMUD, FOZIA M

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/869,612

Applicant(s)

GIANNI, ALESSANDRO MASSIMO

Examiner

Fozia M Hamud

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 Dec 6 2004
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2,5-13,18-26,56 and 57 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2,5-13,18-26,56 and 57 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Response to Amendment

1a. Receipt of Applicant's amendment and arguments, filed on 13 December 2004, is acknowledged.

1b. Claims 1, 3-4, 14-17, 27-55 have been cancelled. Claims 2, 5-13, 18-26 and 56-57 are pending and under consideration.

1b. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim rejections-35 USC § 112:

2a. The rejection of claims 2, 5-13, 18-26, 56-57 made under 35 U.S.C. 112, first paragraph is maintained and for reasons of record set forth in the office actions mailed on 21 October 2003 and 15 June 2004. This rejection is reformulated.

Reciting the limitation "derivatives having the activity of growth hormone" in claim 2 obviates this rejection so far as the recitation of "derivatives" is concerned. Because as was pointed out in the previous office action (mailed on 21 October 2003 and 15 June 2004, page 4), not all derivatives of growth hormone are agonists of growth hormone.

However, this rejection is maintained in so far as the recitation of "any factor inducing growth hormone release", is concerned, because this limitation is not enabled, for the following reasons.

Applicant argues that the fact that applicant does not have working examples of a factor inducing growth hormone release", should not be reason for lack of enablement as applicant is allowed to be prophetic for the subject matter claimed. Applicant further

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argues that factors that induce the release of growth hormone were well known at the time the invention was made, as evidenced by Appendix A (submitted on 03/17/2004) listing prior art references disclosing such factors and the attached front pages of U.S. patents relating to growth hormone releasing hormone. Thus, Applicant concludes that the claimed invention is fully enabled. Applicant submits that all that is required to satisfy the enablement requirement is that one of skill in the art finds it credible that any factor inducing growth hormone release would reasonably be expected to have the same effect as growth hormone itself on enhancing the mobilization or peripheralization effect of G-CSF. Applicant argues that it would be reasonable to expect that administering a factor that induces growth hormone release would have similar effects to administering growth hormone per se since growth hormone would be released in the subject as a result of the administration of the inducing factor. Applicant contends that he has discovered the unexpectedly superior result that growth hormone enhances the effect of G-CSF and that since factors that release growth hormone are well known in the art, and the instant specification specifically teaches such use in the instant application.

These arguments have been fully considered but are deemed persuasive in part. The amendment of claim 2 to recite "... growth hormone derivative having the activity of growth hormone ...", obviates the enablement rejection for "derivatives". However, although working examples are not necessary for enablement under 112, first paragraph, they are one of the factors to be considered, when evaluating enablement requirements. In the instant case, Applicant has not shown that "growth hormone

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releasing factors" enhance the "mobilization or peripheralization effect of G-CSF" to increase the number of circulating CD34+. Furthermore, this limitation encompasses known factors as well as factors that are yet to be discovered. Accordingly, it will be undue experimentation to determine all the encompassed factors and test which ones might work synergistically with G-CSF in increasing the number of CD34+ circulating cells. The regulation of growth hormone secretion and its action at target tissues is a very tightly controlled and complicated system. Therefore, one of ordinary skill in the art would not expect, a factor that releases growth hormone would actually have the same effect as growth in mobilization or peripheralization effect of G-CSF, since applicant has not shown one single example and prior art is silent on the subject. Applicant is correct in that he is allowed to be prophetic for the subject matter claimed, however, Applicant is required to show that a representative number of the encompassed growth hormone releasing factors work synergistically with G-CSF in increasing circulating CD34+ cells. The issue is not the existence of growth hormone releasing factors, but the fact the Applicant has not shown one single growth hormone releasing factor which increases the circulating CD34+ cells when administered in conjunction with G-CSF. Therefore, the disclosure that the administration of rhGH in conjunction with G-CSF stimulates the mobilization of CD34+ cells, is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims which encompass "all" possible factors that induce growth hormone release.

2b. The rejection of claims 2, 5-13, 18-26 made under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, set forth in the office action

mailed on 21 October 2003, pages 7-8, and withdrawn in the office action mailed on 15 June 2004, is hereby reinstated. Claims 56-57 are also rejected under this statute. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In the response file on 17 March 2004, Applicant provides the numbers of U.S. Patents that disclose growth hormone releasing hormone, as well as a listing of factors in Appendix A which have been shown to induce growth hormone release in the prior art, to provide written description for claim 2 so far as it pertains to "any factor inducing growth hormone release". Applicant concludes, while the present specification itself provides an adequate written description, this is supplemented by the wealth of knowledge in the prior art about derivatives of growth hormone and a factor inducing the release of growth hormone.

This argument is not found persuasive, because, "any factor inducing growth hormone release" recited in claim 2, encompasses the factors listed in Appendix A, as well as factors not yet discovered. Neither the instant specification nor the claim 2 describes the structure of "any factor inducing growth hormone release", the recited factor is only described by function.. The skilled artisan would not be able to visualize the structure of all the factors that induces the release, as encompassed by claim 2. Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed. As a result, it

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does not appear that the inventors were in possession of any factor that induces the release to be used in the claimed method.

2c. Claims 2, 5-13, 18-26 and 56-57 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of administering growth hormone and G-CSF in ~~✓~~ BALB/C mice and studying the total CFU-C or BFU-E activity circulating in the peripheral blood; and a method of administering growth hormone and G-CSF in cancer patients undergoing chemotherapy, and counting the number of CD34+ cells in blood, is not enabling for a method of preparing CD34+ cells *in vivo*, by administering to a donor a composition comprising "any factor inducing growth hormone release", with a composition comprising G-CSF, and isolating CD34+ of circulating cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, practice the invention commensurate in scope with these claims.

Claim 2 is interpreted as being drawn to a method of preparing a population of CD34+ cells from a donor that was administered G-CSF and growth hormone and isolating said cells and donating the cells to a recipient. The instant specification discloses that administering growth hormone and G-CSF to cancer patients undergoing chemotherapy increases the number of CD34+ circulating cells, (see examples 2 and 7 and table 1). However, the instant specification does not disclose a donor receiving growth hormone or its derivatives or any factor inducing growth hormone with G-CSF and demonstrate that CD34+ circulating cells as well as all the cells recited in claims 7, 8, 9, 11, 12 are increased. The state of the art recognizes that 3-10 µg/kg of G-CSF

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stimulates progenitor stem cells in human healthy donors, (see Haas). Also Murphy et al teach that 20µg of rhGH every other day for seven days, increased the hematopoietic progenitor cells in mice suffering from combined immune deficiency syndrome.

Therefore, the claimed method in so far as it pertains these dosages of growth hormone and G-CSF is enabled, because the prior art renders it obvious and also teaches the motivation to design it, (see paragraph 3 of this office action). However, one of ordinary skill in the art would not be able to practice the method recited in claim 2, because he/she would not know how much dosage of G-CSF or growth hormone to administer to the donor, because the claim does not recite said dosages. Furthermore, the specification does not disclose what dosage of these agents to administer to a donor, because it only discloses the administration of these agent to cancer patients. Example 7 teaches that 5 µg/kg G-CSF and 33 µg/kg of rhGH are administered on day 7 after chemotherapy. Therefore, the skilled artisan would only know to use the dosages of G-CSF and growth hormone disclosed in the prior art, since the instant specification does not disclose which dosages of G-CSF and growth hormone to administer to a donor.

Claim 2 recites”isolating a population of CD34+ cells which regenerate hematopoiesis in vivo.....”, if these cells are intended to be donated to a patient, then the instant specification is non enabling for donating said cells to a patient, because it does not disclose a recipient that received cells that have been isolated by the claimed method. Transplantation of progenitor cells is a very complex and serious endeavor. The proper healthy donors have to be identified, as well as the proper patients. Schmitz et al teach the transplantation of allogenic peripheral blood progenitor cells that have

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been harvested from healthy donors receiving 5-10 µg/kg of G-CSF to patients who suffered from advanced leukemia. The instant disclosure does not address what type of recipients are these cells intended for.

Therefore, the instant specification is only enabling for a method of administering growth hormone and G-CSF in a BALB/C mice and studying the total CFU-C or BFU-E activity circulating in the peripheral blood; and a method of administering growth hormone and G-CSF in cancer patients undergoing chemotherapy, and counting the number of CD34+ cells in blood.

Claim rejections-35 USC § 103:

3a. The rejection of claims 2, 5-13, 18-26, 56-57 made under 35 U.S.C. 103(a) as being unpatentable Haas et al (1995) in view of Murphy et al (1992), is maintained for reasons of record set forth in the office action mailed on 21 October 2003 and 15 June 2004.

Applicant argues that he does not argue against the disclosure of Haas as applied by the examiner because this is in fact the state of the art that the present invention seeks to improve with applicant's surprisingly superior results. Rather, applicant disagrees with the examiner's interpretation of Murphy's disclosure and its application to suggest that the administration of the G-CSF of Haas and the growth hormone of Murphy together would be expected to have synergistic effect. Murphy teaches only the peripheral engraftment of T cells, which are differentiated or at least partly differentiated in the case of pre-T cells, not hematopoietic progenitor and stem cells. Applicant submits that one of skill in the art would certainly not confuse Murphy's

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teaching regarding T cells as a suggestion that growth hormone would function synergistically with G-CSF for undifferentiated CD34+ hemapoietic progenitor and stem cells (see Haas, page 251, middle of left column, where it is disclosed that the CD34+ antigen is expressed on all human hematopoietic progenitor and stem cells). Applicant concludes that one of ordinary skill in the art would not extrapolate the disclosures of Murphy regarding the action of growth hormone on T-cells with Haas' disclosure of the mobilizing effect of G-CSF on hemapoietic progenitor and stem cells to arrive at the surprising finding that growth hormone enhances the mobilization and peripheralization effect of G-CSF on undifferentiated CD34+ hemapoietic progenitor and stem cells.

This argument is not found persuasive, because, Murphy et al teach that the administration of growth hormone in vivo results in increase in hematopoetic progenitor cells (CD34+ antigen is expressed on all human hematopoietic progenitor and stem cells) and that this effect does not require the production of conlony stimulating factor by T cells, (see page 1444, column 2 and page 1446, column 2). Murphy suggests that rhGH may improve hematopoietic engraftment after bone marrow transplantation or improve hematologic parameters in patients undergoing chemotherapy or radiation therapy, (see page 1447, column 1). Murphy concludes that growth hormone exerts significant hematopoietic effect in vivo and may be of considerable clinical use to augment hematopoiesis in humans (see top of page 1447).

Applicant is correct in that Haas reviews the state of the art regarding the effect of G-CSF on mobilization of hematopoetic progenitor and stem cells. One of the references cited by Haas teaches that the administration of G-CSF in healthy donors

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results in 2.2×10^6 to 8×10^6 CD34+ cells/kg, between 9.8×10^4 to 48.3×10^4 CFU-GM/kg, and 13.2×10^4 to 63.3×10^4 BFU-E/kg, (see Schmitz et al. Blood, Vol.85, No. 6, March 1995, pages 1666-1672, especially page 1669, column 1). Therefore, it does not appear that the results presented in the current application improve the disclosure of Schmitz. The instant specification only discloses the administration of GH and G-CSF to cancer patients undergoing chemotherapy, (see example 2 which discloses the selection of patients and Example 7). Applicant shows that cycle 2 (chemotherapy agent + G-CSF + rhGH) is superior to cycle 1 (chemotherapy agent + G-CSF or cycle 3(chemotherapy alone), see table 2. Therefore, since Applicant does not disclose the administration of rhGH and G-CSF to donors, it does not improve the disclosure of Schmitz, because Schmitz presents the effect of G-CSF on progenitor cells in healthy donors, while the instant specification discloses the effect of rGH and G-CSF from patients undergoing chemotherapy. Furthermore, the cell numbers recited in the instant claims are not superior to that disclosed in Schmitz et al.

Therefore, the combined teachings of Haas et al and Murphy et al render the claimed invention obvious, because Haas et al teach that the administration of G-CSF increased the level of circulating CD34+ cells, and Murphy et al teaches the growth hormone exerts a significant effect on hematopoietic progenitor cell. Thus, one of ordinary skill in the art would have an expectation of success that the administration of these agents together would have synergistic effect.

Claim rejections-35 USC § 112, second:

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4. Claims 2, 5-13, 18-26 and 56-57 stand rejected under 35 U.S.C. 112, second paragraph, and for reasons of record set forth in the office actions mailed on 15 June 2000.

Regarding “..to further increase ..” recited in claim 2, Applicant argues that Example 7 of the instant disclosure shows that following chemotherapy there is a doubling or tripling in the mobilization of circulating CD34+ cells in the blood stream when growth hormone and G-CSF are administered versus when G-CSF is administered alone.

This is not found persuasive, because the claim is not drawn to the administration of G-CSF alone or with growth hormone after chemotherapy, whereby, the number of circulating cells can be compared before or after chemotherapy, with G-CSF alone or with G-CSF and growth hormone.

4a. Regarding claim 7, 12 and 12, “about” was not found indefinite, but “..or more..”, recited in these claims, because it is unclear how much more cells, 1 million, 1 thousand or 1 hundred more, or different, the metes and bounds of the claims cannot be ascertained.

4b. Regarding claim 56, Applicant argues that “..different time “, is set forth in the specification as three times a day for growth hormone and once a day for G-CSF and that one of ordinary skill in the art would know the metes and bounds of the claim.

This is not found persuasive, because it is not clear whether the two agents can be administered right away from one another or whether there should be an interval

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between them and how long. For example, should G-CSF be administered between the growth hormone dosages or before or after them?

New Rejections:

Claim rejections-35 USC § 112, second:

5a. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: it is unclear whether the isolated CD34+ cells are donated to a recipient or whether these cells are stored in appropriate conditions. Appropriate correction is required.

5b. Claim 2 recites “..regenerate hematopoiesis *in vivo*...”, however, it is unclear whose *in vivo* hematopoiesis are regenerated by these cells, the donor’s or a recipient.

5c. Claim 8 recites “.....an increased level of CFU-C....”, however, it is unclear how much of these cells should be increased and compared to what? Again the metes and bounds of the claim cannot be ascertained.

5d. Claims 10 and 12 recite “....or recipient.....”, however, it is unclear which recipient is being referred to, since no recipient is recited in claim 2.

Conclusion:

6. No claim is allowed.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M. Hamud whose telephone number is (571) 272-

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0884. The examiner can normally be reached on Monday, Thursday-Friday, 6:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Fozia Hamud
Patent Examiner
Art Unit 1647
17 March 2005


JANET ANDRES
PRIMARY EXAMINER